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EXAMINER	
FRAZIER, BARBARA S	
ART UNIT	PAPER NUMBER
1611	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/803,187	CHRISTOPH, THOMAS	
	Examiner	Art Unit	
	BARBARA FRAZIER	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-41,57 and 73* is/are pending in the application.

4a) Of the above claim(s) *38,40 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,39,57 and 73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 37-41, 57, and 73 are pending in this application.

2. Cancellation of claims 48, 50, 51, and 54-56 is acknowledged; claims 1-36, 42-47, 49, 52, 53, and 58-72 already stand canceled.

3. Claims 38, 40, and 41 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 9/27/07.

4. Claims 37, 39, 57, and 73 are examined.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. **Claims 37, 39, 57, and 73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.** The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims, as presently amended, are drawn to dosages that provide a synergistic effect for the treatment of urinary incontinence (see claim 37). Page 4 of the specification generally states that the substance combinations show a synergistic effect for treatment of urinary incontinence (page 4, paragraph [0010]). Page 47 teaches amounts of "medicaments" which comprise at least 0.05 to 90.0% of "the active compound" (but does not specify if "the active compound" is only one of the active compounds currently claimed, or their combination), and teaches dosage amounts for the compound of formula I, of which (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol is a species (page 47, paragraph [0054]). However, the specification does not teach dosage ranges for the second compound (oxybutynin, as presently claimed), and in particular, the specification does not teach amounts of each compound **relative to one another** (for example, as ratios of amounts of (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol to oxybutynin) which provide a synergistic effect for the treatment of urinary incontinence. While Example 1 of the specification does teach one dosage amount of each compound which provides a synergistic effect for the treatment of urinary incontinence, it is noted that, while only one dose of each compound in the combination of claim 1 is tested in Example 1 of the specification, the claims are drawn to each compound at any dosage which provides a synergistic effect for the treatment of urinary incontinence. One skilled in the art would reasonably expect synergism to be dose dependent because, if the amount of one of the components is very small, it would not be expected to contribute to the efficacy of the combination. Conversely, if the amount of one of the components is very large, one

skilled in the art would not expect the addition of another component to potentiate the effects of the component present in large amounts. Therefore, one skilled in the art would reasonably expect there to be a range of dosages at which synergism would be provided. Since the specification does not teach any dosage amounts for oxybutynin, nor its amounts relative to the amount of (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol, except for the single dosage amount of Example 1, and Applicant has provided data for only a single dosage of each component in the composition at which synergism is provided, one of ordinary skill in the art would not be in possession of the range of dosages of each compound, relative to one another, at which synergism is provided, as currently claimed.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 37, 57, and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chutka et al. ("Urinary Incontinence in the Elderly: Drug Treatment Options," 1998, Drugs, Volume 56, Number 4, Pages 587-595 and cited by Applicant), in view of Buschmann (US Patent 6,248,737) and Andersson et al ("The pharmacological treatment of urinary incontinence," 1999, British Journal of Urology International, 84:923-947 and cited by Applicant).

The claimed invention is drawn to a composition comprising an admixture of (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol and oxybutynin (see claim 37).

Chutka et al teach that both anticholinergic drugs (i.e., antimuscarinic agents) and opioids can decrease the contraction of the detrusor by impairing the contractility of the detrusor and potentially lead to urinary retention (see, e.g., page 593, third paragraph, and Table 1).

Chutka et al do not specifically teach the combination of an analgesic such as (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride and an antimuscarinic agent such as oxybutynin.

Buschmann ‘737 teach 1-phenyl-3-dimethylaminopropane compounds with an analgesic effect, which are suitable for the treatment of severe pain without giving rise to the side effects which are typical of opioids, and which do not exhibit the side effects, for example nausea and vomiting, which occur during treatment with the opioid tramadol in some cases, and which has a significantly enhanced analgesic effect compared with that of tramadol (col. 1, lines 52-65). Buschmann ‘737 teaches a method of making and separating the (+) enantiomer of (2R, 3R)- 1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol (Example 1, column 6, line 23 to column 7, line 61). Buschmann '737 teaches that the (+) enantiomer of (2R, 3R)-1-dimethylamino- 3-(3-methylphenyl)-2-methylpentan-3-ol is a superior analgesic compared to the racemic mixture or (-) enantiomer (column 23, Table).

Andersson et al teach pharmaceutical substances that are known to treat urinary incontinence (Title) and include anti-muscarinic (i.e., anticholerinergic) agents such as atropine, propantheline, emepronium, trospium, tolterodine, darifenacin, oxybutynin and propiverine (pages 924 and 925, table 2). Andersson et al teach that one such anti-muscarinic agent, oxybutynin, has well documented efficacy in the treatment of detrusor hyperactivity, is available in various forms, and is probably the drug of first choice in patients with detrusor hyperactivity (page 930, column 2, third and fifth full paragraphs).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to combine an admixture of (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride and an antimuscarinic agent; thus arriving at the claimed invention. One skilled in the art would be motivated to do so, with a reasonable expectation success, for the following reasons: First, one skilled in the art would be motivated to combine an opioid and an anticholinergic agent, since both are known to impair detrusor contraction, as taught by Chutka et al. It is *prima facie* obvious to combine two compositions, each of which is taught by the prior art, to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. See MPEP 2144.06. Second, one skilled in the art would be motivated to substitute (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride for an opioid, since the aminopropane compound has an enhanced analgesic effect compared to an opioid (and therefore would be reasonably expected to have the same or improved efficacy in relaxing bladder muscles as well) but without the negative side effects, as taught by Buschmann ‘737. Third, one skilled in

the art would be motivated to select oxybutynin as the antimuscarinic agent because oxybutynin is known to be effective as an antimuscarinic agent, and is even known as the "drug of choice", as taught by Andersson et al.

Regarding claim 57, Buschmann '737 teaches the hydrochloride salt of (+)-(2R,3R)-1-dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol hydrochloride (column 7, Example 2 and column 23, Table).

Regarding claim 73, Buschmann '737 teaches that the analgesics are administered with pharmaceutically suitable auxiliary substances (see col. 5, lines 48-67).

The following rejection is newly applied, necessitated by Applicant's amendment:

9. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chutka in view of Buschmann and Andersson as applied to claims 37, 57, and 73 above, and further in view of Noronha-Blob et al. (J. Pharm. Exp. Ther., 256(2), 562-567, 1991).

Claim 39, as amended, is drawn to the composition of matter of claim 37, wherein oxybutynin is present in the form of a pure enantiomer (see claim 39).

The invention of the combined references is delineated above (see paragraph 8).

The invention of the combined references is silent with respect to the use of an enantiomer of oxybutynin.

Noronha-Blob teaches enantiomers of oxybutynin, and their *in vivo* effects on urinary bladder contraction (abstract). Noronha-Blob teaches that the activity of the

racemate of oxybutynin is attributable to the (*R*) enantiomer for controlling urinary bladder contractions (page 567, 1st column), and shows similar potencies to the racemate (e.g., see page 565, Table 2), but may offer no significant pharmacological advantage over the racemate in terms of its principal therapeutic and side effect profile (abstract).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to select the (*R*) enantiomer of oxybutynin as the form of oxybutynin in the composition of the combined references; thus arriving at the claimed invention. One skilled in the art would have been motivated to do so because the racemate of oxybutynin (assumed to be the form of oxybutynin taught by Andersson, since Andersson does not specify an enantiomeric form) and the (*R*) enantiomer of oxybutynin show the same activity and potencies for controlling urinary bladder contractions, as taught by Noronha-Blob, and therefore are functionally equivalent to one another. Therefore, it would be well within the purview of the skilled artisan to choose either compound as the form of oxybutynin in the composition of the combined references, since the prior art establishes the functional equivalency of the (*R*) enantiomer of oxybutynin and the racemate of oxybutynin.

Response to Arguments

10. Applicant's arguments filed 8/25/10 have been fully considered but they are not persuasive.

Applicants argue that the synergistic effect of the presently claimed composition of matter for the treatment of urinary incontinence is unexpected and demonstrated in Example 1 of the specification. Applicants assert the synergistic effect demonstrated in Example 1 is commensurate with the scope of the claims, and that the unexpected, synergistic effect of the presently claimed composition of matter effectively rebuts any *prima facie* case of obviousness over Chutka et al., Buschmann et al. '737, and Andersson et al.

This argument is not persuasive. It is noted that only one dose of each compound in the combination of claim 1 is tested in Example 1 of the specification, but the claims are drawn to each compound at any dosage which provides a synergistic effect for the treatment of urinary incontinence. As stated previously, one skilled in the art would reasonably expect synergism to be dose dependent because, if the amount of one of the components is very small, it would not be expected to contribute to the efficacy of the combination. Conversely, if the amount of one of the components is very large, one skilled in the art would not expect the addition of another component to potentiate the effects of the component present in large amounts. Therefore, one skilled in the art would reasonably expect there to be a range of dosages at which synergism might occur. Since Applicant has provided data for only a single dosage of each component in the composition, one of ordinary skill in the art would not be able to determine a trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof to any dosage amount of each compound wherein

the amount of each compound relative to the other one provides a synergistic effect. See MPEP 716.02(d).

Therefore, it is the Examiner's position that the claims are rendered obvious.

Conclusion

No claims are allowed at this time.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BARBARA FRAZIER whose telephone number is (571)270-3496. The examiner can normally be reached on Monday-Thursday 9am-4pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BSF

/Ashwin Mehta/
Primary Examiner, Art Unit 1638